**Contraindications**

Levetiracetam is contraindicated in:
- Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

**Special Warnings and Special Precautions for Use**

**Discontinuation**

If Levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 Kg: 500 mg decreases twice daily every two to four weeks; children and adolescents weighing less than 50 Kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks).

**Renal or Hepatic Impairment**

The administration of Levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

**Acute Kidney Injury**

The use of Levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months.

**Blood cell Counts**

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with Levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (see Undesirable Effects).

**Depression and/or Suicidal Ideation**

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including Levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known. Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

**Paediatric Population**

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

**Excipients**

**Oral Solution**

Levetiracetam 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E211) which may cause allergic reactions (possibly delayed).

It also includes maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product. It contains glycerol which may cause, stomach upset and diarrhoea.

**Solution for Infusion**

This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.83 mmol (or 19 mg) per vial). It should be taken into consideration by patients on a controlled sodium diet.

**Interaction with Other Medicinal Products and Other Forms of Interaction**

**Antiepileptic Medicinal Products**

Pre-marketing data from clinical studies conducted in adults indicate that Levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Levetiracetam.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day Levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered Levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20 % higher Levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

**Probenecid**

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of Levetiracetam. Nevertheless, the concentration of this metabolite remains low.

**Methotrexate**

Concomitant administration of Levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and Levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.

**Oral Contraceptives, Digoxin and Warfarin**

Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel), endocrine parameters (lutinizing hormone and progesterone) were not modified. Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not

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**ATC Code**

N03AX14

**Pharmacotherapeutic Group**

Antiepileptics; Other Antiepileptics.

The active substance, Levetiracetam, is a pyrrolidine derivative (S-enantiomer of 2-oxo-1-pyrrolidine acetic acid), chemically unrelated to existing antiepileptic active substances.

The mechanism of action of Levetiracetam still remains to be fully elucidated. In vitro and in vivo experiments suggest that Levetiracetam does not alter basic cell characteristics and normal neurotransmission.

In vitro studies show that Levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, Levetiracetam has been shown in in vitro studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, anion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between Levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

**Therapeutic Indications**

**Levetiracetam is Indicated as Monotherapy in the Treatment of:**

- Partial onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

**Levetiracetam is Indicated as Adjunctive Therapy in the Treatment of:**

- Partial onset seizures with or without secondary generalization in adults, adolescents, children from 4 years of age with epilepsy.
- Myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.
- Primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.
modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of Levetiracetam.

**Laxatives**

There have been isolated reports of decreased Levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral Levetiracetam. Therefore, macrogel should not be taken orally for one hour before and for one hour after taking Levetiracetam.

**Food and Alcohol**

The extent of absorption of Levetiracetam was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of Levetiracetam with alcohol are available.

**Pregnancy and Lactation**

**Fertility**

No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

**Pregnancy**

Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

Post-marketing data from several prospective pregnancy registries have documented outcomes in over 1000 women exposed to Levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity. Physiological changes during pregnancy may affect Levetiracetam concentration. Decrease in Levetiracetam plasma concentrations has been observed in several studies. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with Levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the fetus.

**Lactation**

Levetiracetam is secreted in human breast milk. Therefore, breast-feeding is not recommended. However, if Levetiracetam treatment is needed during breast feeding, the benefit/ risk of the treatment should be weighed considering the importance of breastfeeding.

**Effects on Ability to Drive and Use Machines**

Levetiracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

**Undesirable Effects**

**Clinical Trial Data and Post-Marketing Data**

**Summary of the Safety Profile**

The undesirable effects profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3416 patients treated with Levetiracetam. These data are supplemented with the use of Levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The most frequently reported undesirable effect were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of Levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Undesirable effects are listed below by MedDRA system organ class and by frequency.

**Frequencies are defined as:**

- **Very common** ≥1/10
- **Common** 1/10 to <1/10
- **Uncommon** 1/100 to <1/100
- **Rare** 1/1000 to <1/1000
- **Very rare** 1/10000 or <1/10000
- **Not known** (cannot be estimated from the available data).

**Infections and Infestations**

Very common Nasopharyngitis.

Rare Infection.

**Blood and Lymphatic System Disorders**

Uncommon Thrombocytopenia, leucopenia.

Rare Pancytopenia, neutropenia, agranulocytosis.

**Immune System Disorders**

Rare Drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis).

**Metabolism and Nutrition Disorders**

Common Anorexia.

Uncommon Weight decreased, weight increase.

Rare Hypoanaemia.

**Psychiatric Disorders**

Common Depression, hostility/agression, anxiety, insomnia, nervousness/irritability.

Uncommon Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation.

Rare Completed suicide, personality disorder, abnormal thinking.

**Nervous System Disorders**

Very common Dizziness, headache.

Common Seizure, balance disorder, dizziness, lethargy, tremor.

Uncommon Amnesia, memory impairment, abnormal coordination/ataxia, paraesthesia, disturbance in attention.

Rare Nystagmus, diplopia, vision blurred.

**Eye Disorders**

**Respiratory, Thoracic and Mediastinal Disorders**

Common Cough.

**Gastrointestinal Disorders**

Common Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea.

Rare Pancreatitis.

**Hepatobiliary Disorders**

Uncommon Rare Abnormal liver function tests.

**Renal and Urinary Disorders**

Rare Azotaemia.

**Skin and Subcutaneous Tissue Disorders**

Common Rash.

Uncommon Alopecia, eczema, pruritus.

Rare Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme.

**Musculoskeletal and Connective Tissue Disorders**

Uncommon Muscle weakness, myalgia.

Rare Rhombomylitis and blood creatine phosphokinase increased.

**General Disorders and Administration Site Conditions**

Common Asthenia/fatigue.

**Injury, Poisoning and Procedural Complications**

Uncommon Injury.

*Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Cases of encephalopathy have been rarely observed after Levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

**Description of Selected Undesirable Effects**

The risk of anorexia is higher when Levetiracetam is co-administered with topiramate.

In several cases of alopecia, recovery was observed when Levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

**Paediatric Population**

In patients aged 4-16 years, a total of 645 patients have been treated with Levetiracetam in placebo-controlled and open-label extension studies. 233 of these patients were treated with Levetiracetam in placebo-controlled studies. These data are supplemented with the post-marketing experience of the use of Levetiracetam.

The undesirable effect profile of Levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of Levetiracetam in adults except for behavioral and psychiatric undesirable effects which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (very common, 3.4%), mood swings (very common, 2.1%), affect lability (very common, 1.7%), aggression (very common, 8.2%), abnormal behaviour (very common, 5.6%), and lethargy (very common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Levetiracetam was not different (non inferior) from placebo with regard to the change from baseline of the Leiter R Attention and Memory, Memory Screen Composite score in the per-proto-col population. Results related to behavioral and emotional functioning indicated a worsening in Levetiracetam treated patients on aggressive behaviour as measured in a standardized and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took Levetiracetam in the long term open label follow-up study, did not experience a worsening, on average, in their behavioral and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

**Incompatibilities**

None.

**Posology and Method of Administration**

Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

**Film-Coated Tablets**

The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.
Oral Solution
The oral solution may be diluted in a glass of water or baby’s bottle and may be taken with or without food. The daily dose is administered in two equally divided doses.

Concentrate for Solution for Infusion
Levetiracetam concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 mL of a compatible diluent and administered intravenously as a 15-minute intravenous infusion (see Instructions for Use and Handling).
There is no experience with administration of intravenous Levetiracetam for longer period than 4 days.
Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Adults

Monotherapy

Adults and Adolescents from 16 Years of Age
The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on Therapy

Adults (≥18 years) and Adolescents (12 to 17 years) Weighing 50 Kg or More
The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Children

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.
The tablet formulation is not adapted for use in infants and children under the age of 6 years. Levetiracetam oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 Kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Levetiracetam oral solution should be used.
The safety and efficacy of Levetiracetam concentrate for solution for infusion in infants and children less than 4 years of age have not been established.

Monotherapy

The safety and efficacy of Levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.
There are no data available.

Add-on Therapy

Add-on Therapy for Children (4 to 11 years) and Adolescents (12 to 17 years) Weighing Less than 50 Kg
Levetiracetam oral solution is the preferred formulation for use in children under the age of 6 years. For children 6 years and above, Levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets. The initial therapeutic dose is 10 mg/Kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/Kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/Kg twice daily every two weeks. The lowest effective dose should be used.
Dose in children 50 Kg or greater is the same as in adults.

Dose recommendations for children from 4 years of age and adolescents

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose 10 mg/Kg twice daily</th>
<th>Maximum dose 30 mg/Kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Kg (1)</td>
<td>100 mg (1 mL) twice daily</td>
<td>300 mg (3 mL) twice daily</td>
</tr>
<tr>
<td>15 Kg (2)</td>
<td>150 mg (1.5 mL) twice daily</td>
<td>450 mg (4.5 mL) twice daily</td>
</tr>
<tr>
<td>20 Kg (3)</td>
<td>200 mg (2 mL) twice daily</td>
<td>600 mg (6 mL) twice daily</td>
</tr>
<tr>
<td>25 Kg (4)</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 Kg (5)</td>
<td>500 mg daily</td>
<td>1500 mg daily</td>
</tr>
</tbody>
</table>

1) Children 25 Kg or less should preferably start treatment with Levetiracetam 100 mg/mL oral solution
2) Dose in children and adolescents 50 Kg or more is the same as in adults

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal Impairment

The daily dose must be individualized according to renal function (see Special Warnings and Special Precautions for Use).

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient’s creatinine clearance (Clcr) in mL/min is needed. The Clcr in mL/min may be estimated from serum creatinine (mg/dL) determination, for adults and adolescents weighing 50 Kg or more, using the following formula:

\[
\text{Clcr (mL/min)} = \frac{140 - \text{age (years)}}{72} \times \frac{\text{weight (kg)}}{\text{serum creatinine (mg/dL)}} \times 0.85 \text{ (for women)}
\]

Then Clcr is adjusted for body surface area (BSA) as follows:

\[
\text{Clcr (mL/min/1.73m²)} = \frac{\text{Clcr (mL/min)}}{\text{BSA subject (m²)}} \times 1.73
\]

Dosing adjustment for adults and adolescent patients weighing more than 50 Kg with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (mL/min/1.73 m²)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;80</td>
<td>500 to 1500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50 - 79</td>
<td>500 to 1000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30 - 49</td>
<td>250 to 750 mg twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>250 to 500 mg twice daily</td>
</tr>
</tbody>
</table>

1) A 750 mg loading dose is recommended on the first day of treatment with Levetiracetam. For children with renal impairment, Levetiracetam dose needs to be adjusted based on the renal function as Levetiracetam clearance is related to renal function.

Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 mL/min/1.73 m².

Overdose

Symptoms and Signs
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses.

Treatment
There is no specific antidote for Levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyzer extraction efficiency is 80% for Levetiracetam and 74% for the primary metabolite.
Further management should be as clinically indicated or as recommended by the national poisons center, where available.

Special Precautions for Storage
Do not store above 30°C. Keep out of the reach of children.

Presentations

Levetiracetam, 100 mg/mL Concentrate for Solution for Infusion
Table presents the recommended preparation and administration of Levetiracetam concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg in two divided doses.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Withdrawal Volume</th>
<th>Volume of Diluent</th>
<th>Infusion time</th>
<th>Frequency of administration</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>2.5 mL (half 5 mL vial)</td>
<td>100 mL</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>500 mg/day</td>
</tr>
<tr>
<td>Dose</td>
<td>Withdrawal Volume</td>
<td>Volume of Diluent</td>
<td>Infusion time</td>
<td>Frequency of administration</td>
<td>Total Daily Dose</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>500 mg</td>
<td>5 mL (one 5 mL vial)</td>
<td>100 mL</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td>1000 mg</td>
<td>10 mL (two 5 mL vials)</td>
<td>100 mL</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>2000 mg/day</td>
</tr>
<tr>
<td>1500 mg</td>
<td>15 mL (three 5 mL vials)</td>
<td>100 mL</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>3000 mg/day</td>
</tr>
</tbody>
</table>

This medicinal product is for single use only, any unused solution should be discarded.

This medicinal product must not be mixed with other medicinal products except those mentioned below. Levetiracetam concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15°C - 25°C.

**Diluents**

- Sodium chloride (0.9 %) injection.
- Lactated Ringer’s injection.
- Dextrose 5 % injection.

Medicinal product with particulate matter or discoloration should not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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- Made by: Aesica Pharmaceuticals S.R.L., Pianezza, Italy.

**Based on**

NCDS08 (29-June-2017)